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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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09/994,412

11/27/2001

Ulrich Certa

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09/06/2006

HOFFMANN-LA ROCHE INC.  
PATENT LAW DEPARTMENT  
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NUTLEY, NJ 07110

EXAMINER

CHONG, KIMBERLY

ART UNIT

PAPER NUMBER

1635

DATE MAILED: 09/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

|                              |                               |                              |  |
|------------------------------|-------------------------------|------------------------------|--|
| <b>Office Action Summary</b> | Application No.<br>09/994,412 | Applicant(s)<br>CERTA ET AL. |  |
|                              | Examiner<br>Kimberly Chong    | Art Unit<br>1635             |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 16 June 2006.
- 2a) ☐ This action is FINAL.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-6 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/16/2006 has been entered.

### ***Status of Application/Amendment/Claims***

Applicant's response filed 06/16/2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 03/23/2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-6 are pending and currently under examination in the application.

Art Unit: 1635

***Priority***

Receipt is acknowledged of a certified copy of the EPO 00126113.0 application submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heifetz (WO 99/61631 cited on Form PTO-1449 filed 08/26/2002) in view of Lundstrom K. (cited on Form PTO-892 filed 09/7/05).

The instant claims are drawn to a process for inhibiting expression of a target gene in cells or tissues comprising infecting said cells or tissue with a first set of viral particles expressing a sense RNA strand and a second set of viral particles expressing an antisense RNA strand, wherein the cells or tissue are infected with equal amounts of viral particles, wherein the sense and antisense RNA strands comprise homologous nucleotide sequences to a portion of said target gene, wherein the virus is an alphavirus, wherein the target gene is eukaryotic, viral or synthetic and the homologous nucleotide sequence is at least 50 bases in length and is specific for a target gene.

Heifetz et al. teach a process for inhibiting expression of a gene in a plant cell by administration of a sense RNA fragment of a target gene and an antisense RNA

Art Unit: 1635

fragment of a target gene, which are administered into the cell sequentially (see page 7). Heifetz et al. teach viral vectors are used to introduce said RNA fragments into the plant cells (see page 11). Heifetz et al. further teach the target gene is a plant developmental gene or a plant enzyme (see page 5) and the ribonucleic acid sequences are desirably at least 50 bases in length (see page 11). Heifetz et al. does not teach the viral vector is an alphaviral vector.

Lundstrom teach alphavirus vectors, such as Semliki Forest Virus vectors, for production of high titer viral particles comprising nucleic acid sequences for delivery to cells (see page 680).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use an alphavirus vector, as taught by Lundstrom, to deliver the sense and antisense RNA fragment to plant cells, as taught by Heifetz et al. because Lundstrom teach alphavirus vectors allow direct non-viral transfection of cell lines that results in higher fold expression levels compared to DNA vectors.

One would have been motivated to use alphavirus vector for delivery of sense and antisense RNA strands because Lundstrom specifically teach alphavirus are known for their extremely broad host range and therefore capable of infecting numerous cell types (see page 680 and Table 1). Lundstrom teach RNA molecules are in vitro transcribed from the plasmid vectors (see Figure 1) and alphavirus vectors are easy to produce and have the ability to produce high titer viral particles that make them favorable for gene therapy applications (see page 680).

Art Unit: 1635

Finally, one would have a reasonable expectation of success because Lundstrom teach generation of alphavirus vectors, production of alphavirus particles and use in gene transfer into cells. Further Lundstrom teach an efficient high titer alphavirus viral particle packaging system.

Neither Heifetz et al. or Lundstrom specifically teach infection of cells with equal amounts of an antisense or sense RNA fragments or equal amounts a viral particle consisting of a RNA sense fragment or antisense RNA fragments and a alphavirus vector.

Heifetz et al. teach treating plant cells with a sense RNA and an antisense RNA strand for the purposes of generating dsRNA molecules for interference of expression of a target gene and teach delivery of these sense and antisense RNA strands sequentially to cells wherein the sense and antisense strands form dsRNA, therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use equal amounts of sense and antisense RNA strands and infect cells with equal volumes of viral particles comprising sense and antisense RNA strands for the purposes of forming a dsRNA molecule. One of skill in the art would have motivated to use equal volumes of a viral particle comprising a sense RNA and a viral particle comprising an antisense RNA to allow efficient formation of dsRNA molecules for the purposes of interfering with gene expression.

Applicant argues, in the reply filed 06/16/2006, Heifetz et al. does not teach the use of 'viral particles' for the introduction of RNA fragments into plant cells. First, it must be noted that Applicant's arguments are against the Heifetz et al. reference (WO

Art Unit: 1635

00/68374) cited in the previous office action filed 03/23/2006 and not against the currently cited Heifetz et al. (WO 99/61631) reference. However, because the currently cited Heifetz et al. reference (WO 99/61631) discloses the same invention, Applicant's arguments are relevant and will be addressed in the interest of compact prosecution. Applicant further argues Heifetz et al. do not disclose or suggest the step of administering to the cells or tissue both a first set of viral particles consisting of a single stranded RNA expressing a sense RNA strand and a second set of viral particles consisting of a single stranded RNA expressing an antisense RNA strand.

The specification as filed discloses a 'viral particle' as encompassing "... a ss RNA strand comprising a homologous nucleotide sequence to a portion of the target gene, and the vector of the alphavirus into which the ss RNA is cloned." Heifetz et al. teach administering a sense strand and an antisense strand to alter the expression of a target gene and using a viral vector to delivery the sense and antisense RNA strands to cells and Lundstrom provide motivation for using an alphavirus viral vector and therefore Heifetz et al. in view of Lundstrom teach administration of a viral particle comprising a sense and an antisense RNA strand as defined in the specification. Further Heifetz et al. teach administering both a sense RNA and an antisense RNA sequentially to the cell for the formation of dsRNA inside the cell.

Thus, absent evidence to the contrary the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

***Response to Applicant's Arguments***

The rejection of record of claims 1 and 4-6 under 35 U.S.C. 102(b) as being anticipated by Heifetz et al. (WO 00/68374) is withdrawn in response to Applicant's perfection of priority of EPO 00126113.0.

The rejection of record of claims 1 and 3-6 under 35 U.S.C. 103 as being anticipated by Heifetz et al. (WO 00/68374) in view of Lundstrom, K. is withdrawn in response to Applicant's perfection of priority document EPO 00126113.0.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your

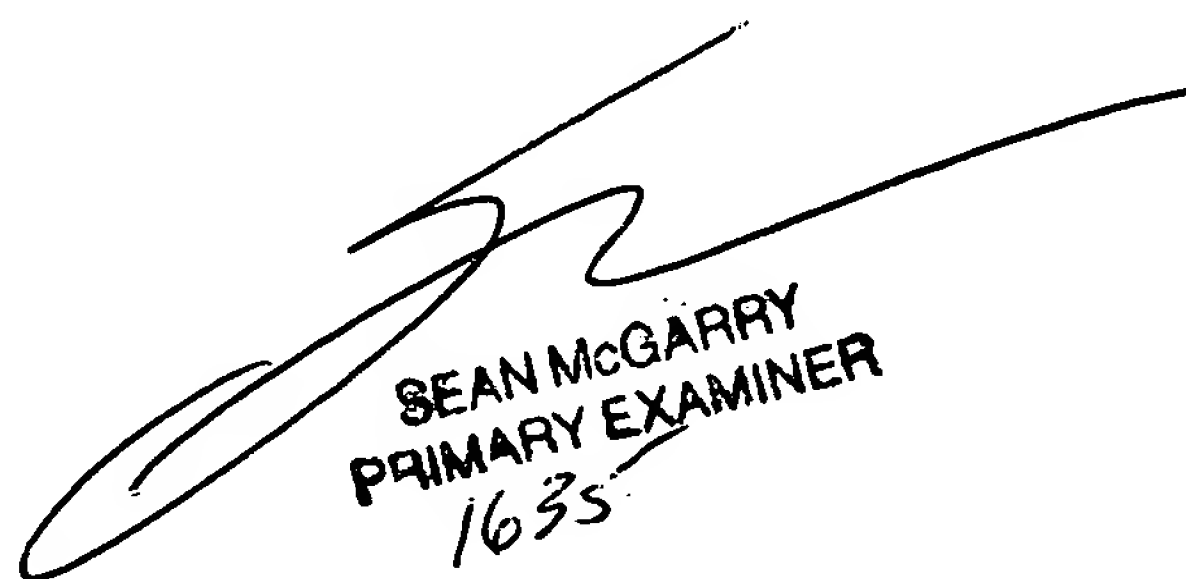


Art Unit: 1635

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Kimberly Chong  
Examiner  
Art Unit 1635



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PRIMARY EXAMINER  
1635